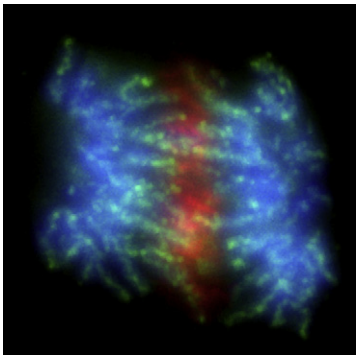
Cell

Chromatin Organization

Although the Victorian proverb "everything in its place and a place for everything" is meant for orderly households, it could just as easily describe the organization of eukaryotic genomes. This issue's Select profiles articles that reveal new insights into how DNA is packaged and partitioned into three-dimensional (3D) structures throughout the life of a cell, shedding new light on how inter- and intrachromosomal interactions influence gene expression and inheritance.



When chromosomes (blue) start to separate at anaphase, Aurora B (red) moves toward the center of spindle, where condensin (green) accumulates on chromosome arms. Image courtesy of Y. Watanabe.

Keeper of Condensation

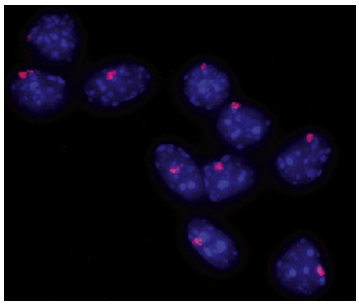
The highly condensed mitotic chromosome is one of the most well-known examples of complex chromatin organization. The redistribution of the mitotic phase kinase, Aurora B, from centromeric foci in metaphase to a midzone cloud in anaphase has long been suspected to promote chromatin condensation in mitosis. To test this prediction, Tada et al. (2011) investigate the spatiotemporal regulation of mitotic chromosome structure and show how Aurora B collaborates with the multiprotein complex condensin to keep chromosomes tightly folded during mitosis. Previous studies suggest that Aurora B phosphorylates kinetochore proteins, which in turn destabilize erroneous microtubule attachment and promote correct chromosome orientation. Now, with a series of elegant genetic and biochemical experiments, the authors demonstrate that Aurora B directly phosphorylates condensin, driving it to specific sites along mitotic chromosomes, including the centromere. Addressing how condensin associates with chromatin, Tada and colleagues clearly show that the N-terminal tails of H2A histones recruit Aurora B-phosphorylated condensin along the entire length of each chromosome; this is especially important for accurate segregation of chromosomes during anaphase. Combining their data with previous observations about Aurora B localization, the authors propose a model in which the anaphase cloud of Aurora B phosphorylates cytoplasmic condensin to promote its interaction with regularly arrayed histones and ensure continued condensation of chromosome arms. This new model provides a likely explanation for why chromosomes with longer arms condense more than those with shorter arms.
Tada, K., et al. (2011). Nature 474, 477–483.

Staying Alive by Silencing Telomeres at the Periphery

Gene expression and inheritance requires specific organization of DNA within the nucleus. A recent study from Chan et al. (2011) sheds new light on how another aspect of biology—genome stability—is influenced by chromatin organization. Packaging of repetitive DNA regions into silent chromatin can help to maintain their stability, prevent deleterious recombination events, and promote normal cellular life span. Highly repetitive DNA elements, including ribosomal DNA (rDNA) and telomeres, are often clustered with the inactive heterochromatin attached to the inner edge of the nuclear envelope. In this study, the authors probe how the cohibin complex, a v-shaped heteromer known to assemble and anchor rDNA to the nuclear periphery, influences the structure and organization of telomeres. With a combination of yeast genetics, chromatin immunoprecipitations, and microscopy, the authors expand the role of cohibin, showing that, in addition to linking inner-nuclear membrane proteins with rDNA, it also connects telomeric DNA to inner-nuclear membrane proteins, anchoring it to the perinuclear region. Distinguishing the cohibin-telomere interaction from that of cohibin-rDNA, Chan and colleagues uncover that cohibin recruits telomeres to the nuclear periphery in an Sir2-dependent manner, with cohibin stabilizing the association between Sir2 and telomeric DNA and enhancing the efficiency of deacetylation, compaction, and inactivation of telomeric DNA. The authors go on to show that DNA stability provided by this subtelomeric silencing, which operates downstream of telomere length control, determines cellular life span. Viewed amidst the backdrop of other studies linking perinuclear localization with a heterochromatic state, this paper solidifies the connection between spatial organization of DNA in the nucleus, its shape, and its transcriptional status.
Chan, J.N., et al. (2011). Dev. Cell 20 867–879.

Xist-ing in the 3D Neighborhood

Inactivated X chromosomes are another example of how heterochromatin is arranged within the nucleus. To balance the dosage of X-linked genes, one of the X chromosomes in female mammalian somatic cells is coated with the long noncoding RNA Xist and stably silenced. How Xist deposition, chromatin structure, and gene silencing are linked remains an open question. In a recent study, Splinter and colleagues develop a method to interrogate 4C chromosome conformation capture data in an allele-specific manner and generate a genome-wide high-resolution map of the inactive (X_i) and active (X_a) X chromosomes. When the authors examine four specific loci on the X_a, they find that these genes display a predictable genome-wide pattern of *cis* and *trans* interactions. Unlike their X_a counterparts, X_i-encoded genes show no preference for their 3D neighbors, except for the few X_i genes that escape inactivation and show looping patterns similar to those of X_a active genes. Surprisingly, when the authors conditionally deplete Xist from cells after X inactivation has been established, they find that, although the majority of X_i genes remain silenced, the X_i assumes an architecture that is reminiscent of X_a. These data indicate that the Xist-mediated X_i-specific chromosome conformation is not essential for the prolonged inactivation of genes in somatic cells and raise the possibility that Xist-induced chromosome folding may be important



Xist RNA clouds (red) visualized in DAPI-stained nuclei of female neural precursor cells (blue). Image courtesy of E. Splinter.

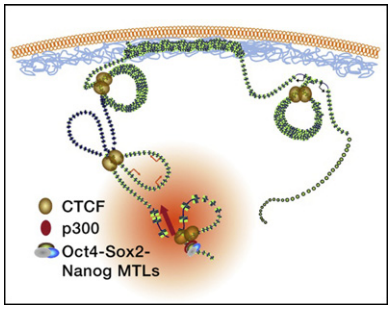
during the establishment of X inactivation. Going forward, it will be interesting to determine whether gene expression and chromosome structure are separable on other chromosomes.
Splinter, E., et al. (2011). Genes Dev. 25, 1371–1383.

Cell-Specific Nucleosome Fingerprints

The positioning and phasing of nucleosomes influences the accessibility of chromatin for transcription. In a recent study, Valouev et al. (2011) analyze nucleosome position in vitro and in primary human blood cells to determine cell-specific nucleosome profiles. First, the authors isolate granulocytes, as well as CD4+ and CD8+ T cell populations, from the blood of a single human donor; extract and digest the chromatin; and then deep sequence the nucleosome-protected fragments. Analysis of the resulting data sets highlights cell type-specific nucleosome phasing and correlates local changes in nucleosome spacing with epigenetic modifications and transcriptional activity. Despite clear in vitro sequence preferences, nucleosome positioning in vivo is highly flexible, with multiple factors near gene regulatory regions influencing nucleosome patterning, such as stalled RNA polymerase and transcription factors. They also explore how binding of the insulator protein, CTCF, influences nucleosome positioning. Although CTCF sites intrinsically encode high nucleosome occupancy, the in vivo binding of CTCF protein displaces nucleosomes such that these sites are now flanked by tightly packed nucleosome arrays. Importantly, nucleosome organization around CTCF sites also differs among cell types, with the CTCF sites in granulocytes surrounded by more densely packed nucleosomes than those same sites in T- cells. This comprehensive study reveals a comparative genome-wide view of the complex interplay between sequence-based nucleosome preferences, cellular identity, and chromatin factors, which provides a resource for further investigation into nucleosome organization.
Valouev, A., et al. (2011). Nature 474, 516–520.

Five Ways to Organize Your Genome with CTCF

Although the insulator protein CTCF can modulate nucleosome spacing along DNA and thus influence local chromatin structure, scientists are just now beginning to assemble a global view of how CTCF regulates higher-order chromatin structure on a genome-wide scale. Handoko and colleagues now provide insight into how CTCF mediates long-range chromatin interactions that organize the genome and regulate transcription. The authors capture all of the chromatin domains brought together by CTCF in pluripotent mouse embryonic stem cells. With the help of ChIA-PET sequencing, a technique that combines chromatin immunoprecipitation with paired end tag sequencing, they create a CTCF-chromatin interactome that provides an extensive catalog of CTCF-dependent chromatin interactions. The study reveals that, in addition to its known functions, CTCF can bridge enhancers to guide gene expression programs and CTCF-associated interaction produce loops that act as structural and functional barriers. By clustering the CTCF-formed chromatin loops based on their histone modification patterns, the authors uncover five distinct classes of CTCF-associated chromatin and elucidate some of the many links between chromatin structures and transcriptional regulation. The findings extend our understanding of genome organization and plasticity and also offer testable hypotheses for how CTCF directs its various insulating activities.
Handoko, L., et al. (2011). Nat. Gen. 43, 630–638.



CTCF-mediated chromatin domains segregate according to associated gene activities and subnuclear localizations. Image courtesy of C. Wei.

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